providing a plurality of samples of biological material comprising a polypeptide and contained in discrete compartments as separate samples from at least two distinct biological conditions that exhibit differential gene expression,

contacting each of the plurality of samples with an antibody wherein the antibody has been obtained by an immune response to in vivo expression of a gene sequence, and

correlating the reaction between the antibody and the plurality of samples with expression of the gene sequence in the samples.

B1

3. The method of claim 1 wherein the step of contacting the plurality of samples is performed with the antibody is performed with antibodies obtained from the in vivo expression of at least 100 different gene sequences.

B2

Claim Rejections – 35 USC § 112

To simplify and expedite the prosecution of the application, applicant cancels claims 12 and 13 without prejudice and without acquiescence in the pending rejections. The following refers to the individual § 112 items detailed at paragraph 10 of the action.

Referring to subparagraph (a), the term "gene sequence" in claim 1 is sufficiently definite to satisfy the requirements of 35 USC § 112, 2nd paragraph. The first clause of claim 1 is amended to clarify that there is no specific gene sequence being examined. The only requirement of the claim is that the samples of biological material comprise a polypeptide and are samples exhibiting

differential gene expression. This language is definite in the requirement that the biological material comprise a polypeptide and that the sameples reflect differential expression.

Referring to subparagraph (b), in the correlating step, the reaction of a gene expression product contained in any of the plurality of samples is correlated to gene expression by reaction of the antibody and the polypeptide that may be contained in the sample. For example, because the antibodies used in the contacting step of the claim are specifically related, on a one-to-one basis, with the gene sequence that was expressed in vivo to raise the antibody, as described in the specification, the subsequent reaction yields a gene expression profile depending on measuring the reaction between the antibody and the gene expression product contained in the biological sample.

In the example of claim 3, the antibodies may be comprised of 100 different antibodies, each having a one-to-one sequence correlation with one of 100 gene sequences, by introducing each antibody to a series of the biological samples, a gene expression profile is created.

In subparagraph (c), the phrase "two distinct biological conditions that exhibit differential gene expression" is meant to define a situation where biological samples are taken from two distinct conditions. As the Examiner notes, the two conditions could be two different medical conditions, i.e., disease and control samples from a patient, or samples derived from the same copulation at two different points in time for gene expression profiling. The difference in the gene expression product/antibody reaction between the two samples provides the differential gene expression profiling resulting from the practice of the method.

With respect to subparagraph (d), the first paragraph of claim 1 is clarified to simply describe a plurality of biological samples that may exhibit differential gene expression, with this revision, the

antibody and the reference to a gene sequence in the second paragraph is rendered sufficiently definite. This clause is also amended to point out that the antibody is derived from the in vivo expression of a gene sequence. This establishes a one-to-one correlation between the antibody and the gene sequence such that expression profiling is enabled.

The points made at subparagraphs (e) and (f) are rendered moot by the cancellation of the claims.

Referring to paragraph 11, dependent claim 3 is amended to clarify that the 100 antibodies are 100 different antibodies obtained from the in vivo expression of 100 different gene sequences.

The § 112 rejection at paragraph 12 is also rendered moot by the cancellation of this claim.

Iris et al. Does Not Disclose Contacting a Polypeptide in the Samples as is Recited in Claim 1 of the Present Invention and Does Not Use Antibodies Produced by In Vivo Expression of A Gene Sequence.

The pending claims are amended to specify an embodiment of the invention wherein the plurality of samples contains a polypeptide gene expression product that reflects differential gene expression in at least two samples. The reaction with antibodies produced from in vivo expression of a gene sequence, as described in the specification, enables a differential gene expression profiling between two different biological samples. The cited section of the Iris et al. patent does not disclose gene expression profiling using a polypeptide product, but refers only to the detection of an RNA target. The reference to the antibodies used in the arrays of Iris et al., plainly refers to antibodies raised by the conventional administration of a protein in an animal model, and does not refer to

antibodies created by in vivo expression. (Col. 23, lines 33 – 57). Thus, the Iris et al. reference does not anticipate the amended claims under 35 USC § 102(e).

35 USC § 103 – The Pending Claims Cannot be Rendered Obvious Under Section 103 of Title 35 Because a *Prima Facie* Case Cannot Exist Based on a Modification of the Cited References.

Referring to paragraph 14 of the office action, the application still does not name multiple inventors and the provisions of 35 USC § 103 (c) and potential existence of prior art under § 102(e), (f), or (g) does not exist.

Regarding the § 103 rejection of the pending claims over Iris et al. and Bandaru, these references cannot produce a *prima facie* case against claims 1 and 3 of the present invention. Even the most generous combination of these references does not contain each element of the pending claims either alone or through the combination of the two cited references.

Neither of the cited references, alone or in combination, disclose the use of a method for gene expression profiling wherein antibodies are raised from in vivo expression and are thereby correlated on a one-to-one basis with the product expression of the gene sequence such that reaction with a polypeptide in a sample demonstrates expression of the gene. While the Bandaru reference discloses an array having a plurality of addresses, the specific nature of the polypeptide and related gene sequences are known in advance. Even though gene expression analysis can be performed for known quantities, the method of the present invention provides an improvement over this approach because the antibodies can be raised to a large number of gene sequences through in vivo expression in a highly efficient and cost effective manner. With a large population of antibody species, correlated to gene sequence, these antibodies can be tested against biological samples for gene

expression profiling without extensive knowledge of the underlying gene sequence. Once the differential reactivity is identified by the reaction of the antibodies with the biological samples, the gene sequence is thereby identified. Applicant submits that this result is novel and non-obvious above the cited references as is demonstrated by the viabilitiy of the references to establish a *prima facie* case under § 103.

With respect to claim 3, clearly, nothing in Bandaru or Iris et al. disclose the possibility of raising more than 100 antibodies (see claim 3 as amended) from the in vivo expression of 100 different gene sequences. It should be noted that the method of the invention may be applied whether or not the specific disease exhibits known patterns of gene expression because, as is expressly stated in the claim, the method of the invention is directed to analyzing gene expression such that in particular instances differences in gene expression may or may not exist for a particular disease.

The desirability of reacting a number of samples with a large number of antibodies and correlating the results to gene expression is not disclosed by Bandaru, which focuses on the 21109 molecule and no such modification to the teaching of Bandaru can be made without departing from the express purpose of Bandaru. Such a modification would violate the rule explained in In re Gordon, 733 F.2d 900 (Fed. Cir. 1984) wherein the Federal Circuit held that a prior art reference may not be modified in a way that would render the prior art invention unsatisfactory for its intended purpose (See MPEP § 2143.01).

In light of the above, applicant requests favorable consideration and allowance of all of the newly presented claims. If the Examiner has any questions regarding the foregoing, or if the Examiner believes that an interview would facilitate the examination of this application, or if any

additional information is required, the Examiner is invited to contact the undersigned at 949/567-6700, X 7740.

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLP

Dated: March 18, 2003

By: _____
Kurt T. Mulville
Reg. No. 37,194

4 Park Plaza, Suite 1600
Irvine, CA 92614
949/567-6700 X 7740 Telephone
949/567-6710 Facsimile